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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,855	03/06/2002	Patrick T. Prendergast	802_003	8597

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
08/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/091,855	PRENDERGAST, PATRICK T.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-31 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *18-31,33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Amendment received on 06/11/2007, wherein claim 31 has been amended.

Applicant's amendment is sufficient to overcome the rejection of claim 31 under 35 U.S.C. 112, second paragraph, as being indefinite.

Applicant's arguments have been considered, but not found persuasive, all the rejections of record made under 35 U.S.C. 103(a) in the office action dated 12/11/2006 are MAINTAINED. See under response to arguments.

Note: Applicant's elect the species Circiliol which is 5,3',4'-trihydroxy-6,7 dimethoxy flavone as the compound, and gemcitabine as chemotherapeutic agent , and also the election of pancreatic cancer, lung cancer as the type of neoplasia in the reply filed on November 19, 2004.

Claims 18-31, and 33-44 are examined herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-27, 30-33, 37-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. (WO 00/03706) in view of Chinery et al. (WO / 9901118), and further in view of Tsukada et al. (Biochemical and Biophysical Research Communications, Vol. 140, No.3, 1986, pages 832-836).

Francis et al. (WO 00/03706) teach a therapeutic composition comprising a therapeutically efficient amount of a flavonoid type compound of formula (I) in combination with cytotoxic agents in the treatment of tumors. In formula (I) of '706, when R_1, R_5 are H; R_2, R_3 are C1-alkoxy group; R_4 is OH, and R_6 is phenyl group substituted with 2 OH groups results in circiliol of the instant invention. See page 3, lines 23-30. The chemotherapeutic agents such as gemcitabine, nucleotide analogues such as 5-fluoro Uracil are disclosed. See page 6, line12. It is also taught that the flavonoids can be combined with the major cytotoxic agents used in polychemotherapies for solid tumors. Examples of methods of use of the compounds flavonoids of formula (I) with chemotherapeutic agent gemcitabine for the treatment of pancreatic adenocarcinoma, bronchial cancer is also taught. See page 39, line 20-page 40, line 5. In the chemotherapeutic treatment of cancers with cytotoxic agents, flavonoids can be administered at the start of chemotherapeutic treatments, either in a single dosage intake or over several days at the start of these treatments depending on the chemotherapeutic protocol. The flavonoid compounds of formula (I) are administered at doses 5 to 50 mg/kg/day. The flavonoid compound and cytotoxic agent can be administered orally, intravenously etc. See page 4, lines 1-10, lines 20-25; lines 30-33, page 6; pages 16, l7. Francis et al. teach that the flavonoids of formula(I) which encompass circiliol can be combined with gemcitabine in a treatment regimen for the treatment of pancreatic cancer. See page 39, lines 10-15; page 81, claims 2, 5, and 10. The treatment of Neoplasia in the form of solid tumors such as non-small-cell lung

cancers, small cell lung cancer by employing flavonoids of formula(I), and a chemotherapeutic agent is also taught. See page 14, lines 9-12; page 17.

Francis et al. does not explicitly teach the employment of particular flavone, circiliol with chemotherapeutic agent, gemcitabine for the treatment of Pancreatic cancer.

Francis et al. does not explicitly teach the employment of particular flavone, circiliol with chemotherapeutic agent, gemcitabine for the treatment of lung cancer.

Francis et al. do not teach a method of treating pancreatic cancer wherein the compound and/or chemotherapeutic agent are contained in a liposome, and said liposome vehicle can be targeted to tumors.

Chinery et al. (WO/9901118) disclose a method to enhance the cytotoxic activity of an antineoplastic drug comprising administering an effective amount of a antineoplastic drug to a host in combination with an effective amount of an antioxidant such as lipoxygenase inhibitor, flavonoids, and phenolic compounds. See page 6, lines 4 to 15; page 43, lines 7-10. The antioxidants increase the effectiveness and decrease the toxicity of antineoplastic agents. The antineoplastic agents include Fluorouracil, Gencitabine, Tamoxifine etc. See page 45, lines 15-20. Chinery et al. further teaches that conditions such as bone cancer, breast cancer, gastric cancer, pancreatic cancer can be treated using said combination. See page 47, line 5-page 48, line2.

Chinery et al. also teaches that pharmaceutical compositions wherein the active compounds can be in a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers such as

ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polylactic acid can be used. See page 51, lines 18-21. Liposomal suspensions containing the actives, including liposomes targeted to infected cells with monoclonal antibodies to viral antigens are also disclosed.

Tsukada et al. (Biochemical and Biophysical Research Communications, Vol. 140, No.3, 1986, pages 832-836) teach that flavonoid compounds like Cirsiliol is a potent specific inhibitor for arachidonate 5-lipoxygense and suppressed the growth of leukemia cells in human. See abstract; page 834, Fig. 1.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ the particular flavonoid Circiliol and combine with gemcitabine as taught by Francis for the treatment of pancreatic cancer. One would be motivated to combine Circiliol with Gemcitabine because (i) Chinery teaches that antineoplastic drugs such as gemcitabine can be combined with lipoxygenase inhibitor in the treatment of pancreatic cancer (ii) Circiliol is a potent inhibitor of arachidonate 5-lipoxygenase inhibitor according to Tsukada. One would be motivated to use a combination of Circiliol and Gemcitabine for the treatment of pancreatic cancer with the expectation of increasing the effectiveness and decreasing the toxicity of chemotherapeutic agent.

It would have been obvious to a person of ordinary skill in the art at the time of invention to use Cirsiliol as flavone and combine with gemcitabine as taught by Francis for the treatment of lung cancer. One would be motivated to combine Cirsiliol a potent inhibitor of arachidonate 5-lipoxygenase as taught by Tsukada with Gemcitabine because (i) Chinery teaches that antineoplastic drugs can be combined with

lipoxygenase inhibitor in the treatment of cancer (ii) Cirsiliol is a lioxygenase inhibitor. One would be motivated to use a combination of Cirsiliol and Gemcitabine with the expectation of treating lung cancer, with increased effectiveness and decreased toxicity of chemotherapeutic agent.

It would have been obvious to a person of ordinary skill in the art at the time of invention to use liposomal suspensions containing Circiliol or chemotherapeutic agent because Chinery teaches liposomal suspension can be used as pharmaceutical carriers for Gemcitabine and flavonoids. The motivation to use liposomal vehicle containing the chemotherapeutic agent or circiliol is with the expectation of delivering the actives more effectively to the infected cells.

Claim 28 is rejected under 35 U.S.C. 103(a), as being unpatentable over Francis et al. in view of Chinery et al. (WO / 9901118), and in view of Tsukada et al. (Biochemical and Biophysical Research Communications, Vol. 140, No.3, 1986, pages 832-836), as applied to Claims 18-27, 30-33, 37-44 above, and further in view of Wang et al. (US 6,608,026), rejection of record.

Francis et al., Chinery, and Tsukada are applied as discussed above.

The references do not teach the administration of radiation treatment.

Wang et al. teach a combination therapy in the treatment of pancreatic cancer by administering a therapeutically effective amount of peptoid,and the antineoplastic agent such as gemcitabine. See column 12, lines 62-66. Wang further teaches that the peptoid, chemotherapeutic agent and/or radiation may be administered concurrently,

sequentially, in any order, depending on the nature of the disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation. See column 11, line 61-column 12, line 8.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer radiation treatment to a patient undergoing chemotherapy because Wang teaches that chemotherapeutic agent and radiation may be administered concurrently, sequentially in any order. One would be motivated to administer radiation treatment with the expectation of obtaining a beneficial effect of treating cancer more effectively.

Claims 29, and 34-36 are rejected under 35 U.S.C. 103(a), as being unpatentable over Francis et al. in view of Chinery et al. (WO / 9901118), and in view of Tsukada et al. (Biochemical and Biophysical Research Communications, Vol. 140, No.3, 1986, pages 832-836), as applied to Claims 18-27, 30-33, 37-44 above, and further in view of Borisy (US 6,569,853), rejection of record.

Francis et al., Chinery, and Tsukada are applied as discussed above.

The references do not specifically teach that the compounds and/or chemotherapeutic agents are contained in a pharmaceutical formulation which has an enteric coating made of polymers such as poly(lactic-glycolic acid) polyester, cellulose acetate phthalate etc. The references do not teach performing surgery on the patient.

Borisy et al. teach a method of treating a patient having cancer comprising administering chloropromazine and pentamidine. See column 23 , lines 30-35. The

treatment can be performed alone or in conjunction with another therapy such as surgery, radiation, chemotherapy. See column 13, lines 55-65. Borisy further teaches that the formulations for oral use include tablets, which may be coated to release the active drug in a predetermined pattern or it may be adapted not to release the active drug substance until after passage of the stomach (enteric coating). The polymers such as methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcelluolose phthalate etc. are disclosed for enteric coating. See column 15, lines 33-50.

It would have been obvious to a person of ordinary skill in the art at the time of invention to perform surgery on a patient undergoing chemotherapy because Borisy teaches that chemotherapeutic agent and surgery may be administered in conjunction. One would be motivated to perform surgery with the expectation of obtaining a beneficial effect of treating cancer more effectively.

It would have been obvious to a person of ordinary skill in the art at the time of invention to contain the chemotherapeutic agent in pharmaceutical formulation which has an enteric coating using polymers such as cellulose acetate because Borisy teaches that the active agents for the treatment of cancer can be contained in a formulation which has enteric coating. One would be motivated to use enteric coating for containing the active agent with the expectation of delaying the disintegration and absorption of the active agent in the gastrointestinal tract and thereby providing a sustained release of the active.

Response to Arguments

Applicant argues that "Francis '706 discloses a broad spectrum of flavonoids, and provides no guidance which would lead one of skill in the art to select circiliol from among the broad spectrum of flavonoids disclosed therein for combining with a chemotherapeutic agent for the treatment of pancreatic cancer or lung cancer". This argument has been considered, but not found persuasive because Francis et al. teach that the flavonoids of formula(I) which encompass circiliol are combined with gemcitabine in a treatment regimen for the treatment of pancreatic cancer. See page 39, lines 10-15; page 81, claims 2, 5, and 10. Thus even though WO '706 et al. does not exemplify Circiliol as preferred compound, it has been well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. *In re Boe*, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); *In re Fracalossi*, 681 F.2d 792, 794, 215 USPQ, 570 (CCPA 1982); In re Kaslow, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983).

Applicant argues that "Chinery's definition of antioxidants includes but is not limited to the following classes of compounds: (H) inhibitors of lipoxygenases and cyclooxygenases." These remarks have been considered. It is respectfully pointed out that Chinery et al. (WO/9901118) disclose a method to enhance the cytotoxic activity of an antineoplastic drug comprising administering an effective amount of antineoplastic

drug to a host in combination with an effective amount of an antioxidant which broadly includes flavonoids, phenolic compounds, and inhibitors of lipoxygenases. Chinery also teaches a method to enhance the cytotoxic activity of an antineoplastic drug comprising administering an effective amount of a antineoplastic drug to a host in combination with an effective amount of a lipoxygenase inhibitor. Further, according to Tsukada et al. Cirsiliol is a potent specific inhibitor for arachidonate 5-lipoxygense and suppressed the growth of leukemia cells in human. One of ordinary skill in the art would have been motivated to employ a combination of Circiliol, a known lipoxygenase inhibitor, and Gemcitabine for the treatment of pancreatic cancer with reasonable expectation of success of increasing the effectiveness and decreasing the toxicity of chemotherapeutic agent.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Tuesday-Thursday 7.30am-4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SUPERVISORY PATENT EXAMINER